Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1.-32. (cancelled)

33. (currently amended) An *in vivo* method of affinity maturation by auto-inhibited reactivation to obtain a binding molecule that has an enhanced affinity for a target antigen relative to a reference antibody that specifically binds to the target antigen, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a nucleic acid encoding a competitor antibody that can be secreted and that binds to the target antigen with the same specificity as ~~a~~ the reference antibody;

(ii) introducing into the host cells a nucleic acid encoding a reactivator complex that can be secreted and that comprises a reactivator molecule covalently linked to the target antigen;

(iii) introducing into the host cells a library of genes, each of which encodes an auto-inhibited responder complex that can be secreted and that comprises a responder molecule covalently linked to an inhibitor and to a candidate binding molecule that is an antibody, wherein the responder molecule is an enzyme and the inhibitor is an inhibitor of the enzyme;

(b) incubating the host cells under conditions in which the competitor antibody, the reactivator complex, and the auto-inhibited responder library are expressed and secreted, where the responder molecule is activated when a candidate binding molecule competes for binding with the competitor antibody and binds to the target antigen; whereupon the reactivator displaces the inhibitor from the responder complex; and

(c) detecting a signal from the responder molecule that corresponds to a candidate binding molecule affinity for the target antigen that is greater than that of the reference antibody, thereby identifying a candidate binding molecule with an enhanced affinity for the target antigen.

34. (cancelled)

35. (previously presented) The method of claim 33, further wherein the competitor is the reference antibody.

36. (original) The method of claim 35, further wherein the reference antibody is an Fab fragment.

37. (original) The method of claim 35, further wherein the reference antibody is a single chain Fv (scFv).

38. (withdrawn--currently amended) The method of claim ~~34~~ 33, further wherein the candidate binding molecules are single chain Fvs.

39. (previously presented) The method of claim 33, further wherein the candidate binding molecules are Fab fragments.

40. (withdrawn--currently amended) The method of claim ~~34~~ 33, further wherein the candidate binding molecules are single V-region domains.

41. (cancelled)

42. (cancelled)

43. (withdrawn--currently amended) The method of claim ~~34~~ 33, further wherein the candidate binding molecules are hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

44. (withdrawn--currently amended) The method of claim 43, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

45. (withdrawn--currently amended) The method of claim ~~34~~ 33, further wherein the competitor is a nonhuman antibody and the candidate binding molecules comprise antibodies having at least one human variable region.

46. (cancelled)

47. (cancelled)

48. (currently amended) A method of affinity maturation by self-inhibited reactivation to obtain a binding molecule that has a higher affinity for a target antigen than that of a reference antibody that specifically binds to the target antigen, the method comprising:

(a) recombinantly altering a population of host cells by

(i) introducing into the host cells a nucleic acid encoding a competitor antibody that can be secreted and that binds to the target antigen with the same specificity as a the reference antibody,

(ii) introducing into the host cells a nucleic acid encoding an auto-inhibited responder complex that can be secreted and that comprises a responder molecule covalently linked to an inhibitor and to the target antigen, wherein the responder molecule is an enzyme and the inhibitor is an inhibitor of the enzyme,

(iii) introducing into the host cells a library of genes, each encoding a reactivator complex that can be secreted, wherein each gene encodes a reactivator molecule covalently linked to a candidate binding molecule that is an antibody;

(b) incubating the host cells under conditions in which the competitor antibody, the auto-inhibited responder complex, and the reactivator library complex are expressed and secreted, where the responder molecule is activated when a candidate binding molecule

competes for binding with the competitor antibody and binds to the target antigen; whereupon the reactivator displaces the inhibitor from the responder complex; and

(c) detecting a signal from the responder molecule that corresponds to a candidate binding molecule affinity for the target antigen that is greater than that of the reference antibody, thereby identifying a candidate binding molecule with an enhanced affinity for the target antigen.

49. (cancelled)

50. (previously presented) The method of claim 48, further wherein the competitor is the reference antibody.

51. (previously presented) The method of claim 50, wherein the reference antibody is an Fab fragment.

52. (previously presented) The method of claim 50, wherein the reference antibody is a single chain Fv (scFv).

53. (withdrawn--currently amended) The method of claim ~~49~~ 48, further wherein the candidate binding molecules are single chain Fvs.

54. (previously presented) The method of claim 48, wherein the candidate binding molecules are Fab fragments.

55. (withdrawn--currently amended) The method of claim ~~49~~ 48, wherein the candidate binding molecules are single V-region domains.

56. (cancelled)

57. (cancelled)

58. (withdrawn--currently amended) The method of claim ~~49~~ 48, further wherein the candidate binding molecules are hybrid antibodies that have at least one CDR in a V_H or V_L that is different from the reference antibody and is from a natural antibody repertoire.

59. (withdrawn-currently amended) The method of claim 58, wherein the hybrid antibodies have either a V_H or V_L from the reference antibody and the corresponding V_H or V_L from a natural antibody repertoire.

60. (withdrawn--currently amended) The method of claim ~~49~~ 48, further wherein the reference antibody is a nonhuman antibody and the candidate binding molecules are antibodies having at least one human variable region.

61. (cancelled)

62. (cancelled)

63. (previously presented) The method of claim 33, wherein the host cells are prokaryotic.

64. (previously presented) The method of claim 63, wherein the host cells are *E. coli*.

65. (withdrawn) The method of claim 33, wherein the host cells are yeast cells or mammalian cells.

66. (previously presented) The method of claim 48 wherein the host cells are prokaryotic.

67. (previously presented) The method of claim 66, wherein the host cells are *E. coli*.

68. (withdrawn) The method of claim 48, wherein the host cells are yeast cells or mammalian cells.